Adipocytokines, Fat Distribution, and Insulin Resistance in Elderly Men and Women

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Background. The aim of this study was to evaluate the relation between adiponectin and leptin, fat distribution, and insulin resistance in elderly men and women.

Methods. 68 elderly participants (28 men and 40 women) aged 66–77 years, with body mass index (BMI) ranging from 19.83 to 37.18 kg/m^2, participated in the study. In all participants, we evaluated BMI, waist and hip circumferences, sagittal abdominal diameter (SAD), fat mass (FM) by dual energy X-ray absorptiometry, fasting and 2-hour glucose, insulin, homeostasis model assessment of insulin resistance (HOMA), leptin, and adiponectin.

Results. Elderly women had significantly higher circulating levels of adiponectin and leptin compared to men even after adjusting for age, FM, or waist circumference. In men and women, leptin was positively associated, whereas adiponectin was negatively associated, with BMI, indices of body fat distribution, as well as FM and FM%. Both fasting insulin and HOMA showed significant positive correlation with leptin and negative correlation with adiponectin in both sexes. In a step-wise multiple regression model with HOMA as the dependent variable and age, gender, waist circumference, FM, leptin, and adiponectin as independent variables, waist entered the regression first, explaining 19.7% of HOMA variance, leptin was second, and adiponectin was third, explaining each one an additional 10% of variance. In a multiple linear regression analysis, leptin and adiponectin alone explained up to 38% of HOMA variance.

Conclusion. Leptin and adiponectin together seem to be strictly related to insulin resistance in elderly people, independently of body fat and body fat distribution.

ADIPOSE tissue is currently recognized as a hormonally active system that regulates insulin sensitivity via different circulating adipocytokines (1).

Leptin, a peptide synthesized mainly by white adipose tissue, has been related to insulin resistance, independent of the degree of adiposity, in studies conducted in young and middle-aged individuals (2,3). Recently, an association between leptin, insulin, insulin resistance, and the metabolic syndrome, independent of body fat and fat distribution, has been described even in elderly participants (4).

Adiponectin is a novel discovered protein specifically produced by human adipose cells and abundantly secreted in plasma (5,6). In contrast to leptin and other adipocytokines, adiponectin levels are inversely related to the degree of adiposity in both healthy and diabetic participants (5–13). Moreover, adiponectin levels are decreased in some insulin-resistant states such as obesity and type 2 diabetes, and are negatively related to insulin resistance in patients with normal or altered glucose tolerance (5–15). In addition, decreased adiponectin levels have been shown to represent a risk factor for the development of type 2 diabetes (16,17).

A strong relationship may exist between hyperleptinemia as well between hypoadiponectinemia and the metabolic syndrome, at least in young and middle age. However, no one has previously tested, in a population of elderly participants, the joint effects of different adipocytokines on insulin resistance, whereas only a few reports have studied this outcome in younger populations with conflicting results (8,10,14,18).

Therefore, the aim of this study was to evaluate the relation between adiponectin, leptin, total and regional adiposity, and insulin resistance in elderly men and women.

METHODS

Participants

We studied 68 participants (28 men and 40 women) living independently in Verona, Italy, aged 66 to 77 years, with body mass index (BMI) ranging from 19.83 to 37.18 kg/m^2. All individuals were weight-stable in the previous 6 months and had no evidence of cancer, liver, or renal disease. Only 3 men and 3 women reported a history of type 2 diabetes; 2 men and 3 women were newly diagnosed as diabetic and 2 men and 6 women had impaired glucose tolerance, according to the American Diabetes Association criteria (19). None of the participants received insulin, thiazolidinediones, or any hypoglycemic therapy. None of the women were on hormonal replacement therapy. None of the participants engaged in regular physical activity.

All participants gave their informed consent, and the experimental protocol was approved by the Ethical Committee of our University.

Table 1. Characteristics of the Study Population

Characteristics	Women (N = 40) (Mean ± SD)	Men (N = 28) (Mean ± SD)	P
Age (y)	70.58 ± 2.67	71.61 ± 2.17	.084
Weight (kg)	66.57 ± 11.33	78.75 ± 9.83	.001
BMI (kg/m^2)	27.54 ± 4.52	26.85 ± 2.73	.436
Waist circumference (cm)	85.46 ± 10.23	94.89 ± 6.72	.001
Hip circumference (cm)	100.71 ± 7.86	98.59 ± 4.38	.160
WHR	0.85 ± 0.08	0.96 ± 0.04	.001
SAD (cm)	20.89 ± 2.63	22.98 ± 2.44	.001
FM (kg)	27.67 ± 8.21	21.59 ± 5.12	.001
FM (%)	41.77 ± 6.05	27.75 ± 4.58	.001
Fasting glucose (mmo1/L)	5.44 ± 1.37	5.94 ± 1.84	.223
2-hour glucose (mmol/L)	7.18 ± 2.79	6.56 ± 2.26	.354
Insulin (pmol/L)	68.38 ± 35.88	60.34 ± 26.76	.296
HOMA	2.32 ± 1.28	2.36 ± 1.72	.906
Leptin (ng/ml)	18.10 ± 15.33	5.85 ± 3.27	.001
Adiponectin (µg/ml)	17.14 ± 5.41	9.45 ± 3.88	.001

Note: BMI = Body Mass Index; WHR = waist to hip ratio; SAD = sagittal abdominal diameter, FM = fat mass (measured by dual energy X-ray absorptiometry); HOMA = homeostasis model assessment of insulin resistance; SD = standard deviation.

Anthropometric Measurements

With the participants wearing light indoor clothes and no shoes, body weight was measured to the nearest 0.1 kg (Salus scale, Milan, Italy), and height to the nearest 0.5 cm using a stadiometer (Salus stadiometer, Milan, Italy). BMI was calculated as body weight adjusted by stature squared (kg/m^2). Waist, hip, and waist to hip ratio (WHR) were evaluated as previously described (4). Sagittal abdominal diameter (SAD) was measured with a portable, sliding beam, abdominal caliper as the largest anteroposterior diameter between the xyphoid process and the umbilicus while the participants were on a supine position (20).

Body Composition Assessment

Body composition was measured using dual energy X-ray absorptiometry (DEXA) (Hologic QDR 2000, Waltham, MA) (21). Total body fat (FM) was expressed in kg as well as a percentage of body weight (FM%). Daily quality assurance tests were performed according to the manufacturer's direction. Coefficient of variation (CV) for double determination in 11 participants (men and women aged 66–77 years) was 1% for FM and 2.3% for FM%.

Biochemical Analyses

Venous blood samples for metabolic assessments were obtained after an overnight fast. For the oral glucose tolerance test, patients were given a 75 g glucose load. Blood samples for glucose levels were taken at 0 and 120 minutes. Plasma glucose was measured using a compact chemistry analyzer method (Ektachem DT-60; Eastman Kodak, Inc., Rochester, NY). This method had an interassay CV of 2% (22).

Plasma immunoreactive insulin underwent duplicate measurements by double antibody radioimmunoassay using a commercial kit (Diagnostic Products Corp., Los Angeles, CA). Sensitivity was 6 pmol/L, and the intraassay CV was 4.9%. Insulin resistance was estimated by the HOMA (homeostasis model assessment) method (23).

Plasma leptin and serum adiponectin were measured using commercially available RIA kits (Linco Research, Inc., St. Charles, MO). Sensitivity was 0.1 ng/L for leptin and 1 ng/ml for adiponectin; intraassay and interassay CVs were, respectively, 0.7% and 7.8% for leptin and 3.9 % and 8.5 % for adiponectin.

Statistical Analysis

Results are shown as means ± standard deviation (*SD*). Adiponectin and leptin concentrations were not normally distributed and were log-transformed before analysis. Comparison of anthropometric and metabolic variables by gender was done by unpaired *t* test. General linear regression analysis was used to compare adiponectin and leptin levels between genders after adjusting for different covariates. Pearson's correlation was used to test association between variables. Multiple step-wise regression analysis was used to determine the contribution of different variables to adiponectin levels. Different models of stepwise multiple regression analysis were created to test the joint effects of age, gender, waist circumference, FM, adiponectin, and leptin on HOMA.

The level for statistical significance was $p < .05$ throughout the study. All statistical analyses were done using the SPSS statistical package (SPSS, Inc., Chicago, IL) (24).

RESULTS

Elderly women, despite no significant difference in age and BMI, showed significantly higher adiponectin and leptin levels compared to men (Table 1). These differences were still significant even after adjusting for age (adiponectin mean ± standard error [*SE*]: 16.95 ± 0.77 vs 9.37 ± 0.90 µg/ml; leptin mean ± *SE*: 18.10 ± 1.94 vs 5.85 ± 2.28 ng/ml; $p < .001$), for FM (respectively, mean ± *SE*: 17.41 ± 0.76 vs 8.75 ± 0.90 µg/ml and 14.97 ± 1.38 vs 10.10 ± 1.63 ng/ml; $p < .001$), or waist (respectively, mean ± *SE*: 16.13 ± 0.76 vs 10.48 ± 0.90 µg/ml and 21.42 ± 1.58 vs 1.36 ± 1.88 ng/ml; $p < .001$).

In this sample, age was not significantly associated with adiponectin or leptin levels (Table 2). In men, but not in women, a significant negative correlation was found between adiponectin and leptin ($r = -0.465$; $p = .013$). In both sexes, leptin was positively associated with weight, BMI, fat distribution, as well as FM and FM%. In women, adiponectin was negatively related to BMI, waist, WHR, and SAD, whereas, in men, no significant relations were observed; in both sexes, adiponectin was negatively associated with FM and FM%. Fasting insulin and insulin resistance, evaluated by HOMA, showed significant positive correlations with leptin and negative correlations with adiponectin in both sexes (Table 2).

In a step-wise multiple regression analysis, gender alone explained up to 41% of adiponectin, independent of age, FM, waist, insulin, and insulin resistance; HOMA explained an additional 14% of adiponectin (data not shown in Table).

Table 3 shows a step-wise multiple regression analysis, performed to test the relation between HOMA and adiponectin, leptin, age, gender, waist, and FM. Waist entered the regression first, explaining about 20% of HOMA

Table 2. Correlations Between Adiponectin, Leptin, and Age, Anthropometric, Body Composition, and Metabolic Variables, Separately by Gender

	Women ($N = 40$)		Men ($N = 28$)	
	Adiponectin (r)	Leptin (r)	Adiponectin (r)	Leptin (r)
Age	0.140	−0.012	0.053	0.076
Weight	−0.270	0.663***	−0.100	0.467*
BMI	−0.416**	0.660***	−0.180	0.513**
Waist circumference	−0.472**	0.706***	−0.239	0.534**
Hip circumference	−0.164	0.592***	−0.351	0.527**
WHR	−0.523***	0.467***	−0.132	0.394*
SAD	−0.457**	0.703***	−0.160	0.491**
FM	−0.325*	0.734***	−0.398*	0.741***
FM (%)	−0.355*	0.696***	−0.416*	0.764***
Fasting glucose	−0.235	0.364*	−0.305	0.122
2-h glucose	−0.347*	0.259	−0.366	0.152
Fasting insulin	−0.362*	0.633***	−0.610***	0.519**
HOMA	−0.389*	0.647***	−0.611***	0.447*

Notes: ***$p < .001$; **$p < .01$; *$p < .05$.

WHR = waist to hip ratio; SAD = sagittal abdominal diameter; FM = fat mass (measured by dual energy X-ray absorptiometry); FM (%) = fat mass percentage (measured by dual energy X-ray absorptiometry); HOMA = homeostasis model assessment of insulin resistance; BMI = body mass index.

Table 3. Stepwise Multiple Linear Regression Analysis Where HOMA Was the Dependent Variable and Sex, Age, Waist Circumference, FM, Adiponectin, and Leptin Were the Independent Variables in Elderly Men and Women ($N = 68$)

Variables Entered in the Models	r^2	β Coefficient	Sig.
1 Waist circumference	.197	0.458	0.001
2 Waist circumference	.284	0.392	0.001
Leptin		0.318	0.004
3 Waist circumference	.386	0.149	0.228
Leptin		0.459	0.001
Adiponectin		−0.416	0.001

Note: HOMA = homeostasis model assessment of insulin resistance; FM = fat mass (measured by dual energy X-ray absorptiometry); Sig = significance.

variance. Leptin and adiponectin entered the regression respectively as second and third variables, explaining each one respectively another 10% of HOMA variance. However, leptin and adiponectin alone, in a multiple regression analysis, explained up to 38% of HOMA variance (data not shown in Table).

DISCUSSION

Our study clearly shows strong associations between adiponectin, leptin, body fat, and body fat distribution, as well as insulin resistance even in old age. Leptin and adiponectin were significant predictors of HOMA, explaining approximately 40% of HOMA total variance. A gender difference between men and women in adiponectin and leptin levels was still observed in our participants.

A number of studies showing a significant relation between leptin, different anthropometric variables, and total and subcutaneous fat recently have been published on young and middle-aged individuals with a wide range of BMI (2,3). Our results, in contrast with previous reports (25,26), show a strong relation even in elderly participants between leptin and all the indices of obesity, confirming what we have recently observed in another population of elderly nondiabetic women (4).

To our knowledge, only a few studies (7–10) have previously described a negative association in old age between adiponectin, body fat, and indices of body fat distribution. However, these studies often included populations with a wide age range, where elderly participants were often under-represented and pooled together in the analyses with young and middle-aged individuals (7–10). In our study sample, adiponectin was negatively associated with BMI, waist circumference, WHR, SAD, FM, and FM% in women, whereas not always significant correlations were found in men between the same variables, probably due to the small sample size.

The gender difference in adiponectin and leptin levels, previously observed in young and middle-aged participants (2,3,5,6), seem to persist in old age. In fact, in our study, adiponectin and leptin concentrations were greater in elderly women than in men, even after adjusting for age, body fat, and fat distribution. The effect of sex on adiponectin levels seems to be independent of body fat: in our study, gender explained up to 41% of adiponectin levels, independent of age, fat mass, fat distribution, and insulin resistance. Differences in hormonal status as well as genetic influences may explain this sexual dimorphism in adiponectin and leptin levels; adiponectin and leptin seem to be under a complex hormonal control, where different hormones such as testosterone, estrogens, and glucocorticoids may play a role (2,3,5,27,28).

To our knowledge, this is the first study focusing on the metabolic role of two adipocytokines exclusively conducted in a population of elderly men and women. Only a few articles (7–10,14) have previously described a negative association between adiponectin and insulin resistance, although these studies were in populations where elderly participants were often under-represented and analyzed together with younger individuals (7–10,14). In both elderly men and women, we found a significant negative correlation between adiponectin, insulin, and HOMA. Moreover, in our study, leptin displayed significant but positive correlations with insulin and HOMA in both sexes, as previously described in young-to-middle-aged participants (28,29) and in older individuals (4,30).

As adiponectin and leptin are both strictly associated with insulin resistance, we also examined the relation between these two adipocytokines. In our population, a significant correlation between adiponectin and leptin was found in men but not in women. The relationship between these two adipocytokines is still under debate with conflicting results (7,8,18), probably depending on the characteristics of the population studied such as gender, age, BMI, and glucose tolerance status.

To explore the joint relation between these two adipocytokines, body composition, and fat distribution on insulin resistance, we performed a step-wise multiple regression analysis where HOMA was the dependent variable and adiponectin, leptin, gender, age, total adiposity, and body fat distribution were the independent variables. Waist circumference entered the regression first and

explained up to 20% of HOMA total variance. Leptin and adiponectin entered the regression, respectively, second and third, each adding 10% of HOMA variance. Our findings seem to confirm previous studies (31) showing that visceral fat distribution, as evaluated in our study by waist circumference, is the main determinant of insulin resistance. It must be noted that leptin and adiponectin levels each add another 10% of HOMA variance besides waist circumference, suggesting that endocrine activity of adipose tissue may contribute independent of fat distribution to HOMA.

The mechanisms by which adipocytokines influence insulin resistance are multifaceted and, to our knowledge, partial. It seems that excessive adipose tissue, particularly at the omental level, may be detrimental because of an excessive secretion of different fat-derived peptides (1). Only a few studies have previously tried to analyze together the effects of different adipocytokines on insulin resistance in younger populations, and yielded conflicting results (8,10,14,18). The relationship between insulin resistance, adiponectin, leptin, and resistin has recently been examined in a small group of young nondiabetic patients with a wide range of BMI (18). In this study, after adjusting for gender and BMI, HOMA as well as fasting insulin were significantly correlated with leptin and resistin levels, whereas no association was observed between the same variables and adiponectin (18). Matsubara and colleagues (14) in 486 nondiabetic women with a wide age range, found that adiponectin and leptin were significant predictors of both HOMA and insulin levels independent of systolic blood pressure, BMI, and triglycerides. It is interesting to observe that, in our population of elderly participants, both adiponectin and leptin together were significant predictors of HOMA, explaining up to 38% of total HOMA variance. An addictive metabolic role of these two adipocytokines has also been observed in studies with lipoatrophic and obese diabetic mice, where only the concomitant replenishment of adiponectin and leptin completely improved insulin resistance (32).

Several experimental data (2,3,5,6) suggest an important role of adiponectin and leptin on glucose metabolism. Leptin clearly produces an inhibition of glucose-stimulated insulin secretion and impairs glycogen synthesis and lipogenesis (2,3), whereas adiponectin increases insulin sensitivity by increasing tissue fat oxidation and reducing circulating fatty acid levels and intracellular triglyceride content in liver and muscle (5,6). However, in vivo, a complex network of interactions between different adipocytokines and hormones seem to regulate insulin sensitivity (1) so that other adipocytokines, besides adiponectin and leptin, may play a role in the pathogenesis of insulin resistance, even if it must be noted that adiponectin and leptin are among the most serum-representative adipocytokines (1–3,5,6). Thus, future clinical studies should try to consider different adipocytokines at the same time, exploring their reciprocal interactions and effects on insulin resistance.

Some limitations of our study must be recognized. First, the small sample size and the cross-sectional design of the study do not allow the establishment of cause–effect relationships. Second, visceral fat was not measured directly with abdominal computed tomography (CT) scans but only indirectly estimated by anthropometric measurements such as

waist circumference and SAD. However, in elderly participants, we previously described a strong correlation between waist circumference, SAD, and CT visceral fat area (20). Finally, we evaluated only fasting insulin and HOMA as surrogates for insulin resistance. However, fasting insulin and HOMA have been validated as indices of insulin resistance in several clinical and epidemiological studies (23).

Conclusion

Our study shows that leptin and adiponectin are strictly related to adiposity and insulin resistance in elderly people. These two adipocytokines together may act as good surrogates for visceral fat in the complex relationship between adipose tissue and insulin resistance. However, further studies that include wider populations of elderly participants should provide new insights into the relation between adipose tissue and the metabolic syndrome in elderly people.

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